IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Art Unit: 1611
A. VERMA *et al.*	Examiner: LOVE, T.
Appl. No. 10/578,438	Attorney Docket: 044508-5008
§371 Date: 21 March 2007	Confirmation No. 6971
For: **Activation of Hypoxia-Inducible Gene Expression**	Customer No. 09629

PRE-APPEAL BRIEF REQUEST FOR REVIEW

This communication is a request for a Pre-Appeal Brief Conference for formal review of the rejections in the Office Action of 9 September 2009. Specifically, Applicants request formal review of the rejection of claims 11, 13-15, 24-38 as allegedly obvious in view of Teichberg, *et al.* (U.S. Pre-grant Publication No. 2006/0024284) ("Teichberg"), Aminova *et al.* (Aminova, L.R., *et al., J. Biol. Chem.,* 280(5):3996-4003 (2005)) ("Aminova") and Lu *et al.* (Lu, H., *et al., J. Biol. Chem.,* 277(26):23111-23115 (2002)) ("Lu"). Applicants respectfully submit that (1) the Examiner's reliance on Aminova is in clear error, (2) the Examiner's use of inherency to fill in missing gaps in the obviousness rejection is in clear error, (3) the Examiner's failure to establish that the cited references teach each and every element of the claimed invention is in clear error, and (4) that the Examiner's failure to establish any motivation or predictability in combining only prior art references is in clear error.

The inventors have discovered that the listed compounds can promote neovascularization in a subject when administered in doses sufficient enough to induce HIF-1 mediated gene expression. Prior to Applicants' discovery, it was not known, nor did the state of the art suggest, that dosing any of the listed compounds in a subject would induce neovascularization, regardless of the mechanism of action.

The sole rejection is an obviousness rejection in which the Examiner rejected 11, 13-15, 24-38 as allegedly obvious in view of the cited art. The rejection is, in essence, that it would be obvious to one of skill in art to administer pyruvate, oxaloacetate, alpha-ketoisovalerate, alpha-ketoisocaproate, alpha-keto-beta-methylvalerate, methyl esters thereof, ethyl esters thereof or glycerol esters thereof, collectively referred to herein as "the listed compounds," to promote neovascularization in a patient. It is Applicants' position that the only references that qualify as prior art to the application do not support a *prima facie* case of obviousness, because these references fail to teach or suggest the elements of the claimed invention. In addition, the Examiner has failed to establish why one of skill would be motivated to combine the cited references, and that there would be reasonable expectation of success or predictability.

As an initial matter, Applicants note that Aminova does not qualify as prior art to the present application. Aminova has a publication date of 4 February 2005, and, according to the journal's website, was first published on-line on 22 November 2004. The present application was filed as an international PCT application on 8 November 2004 and claims priority to U.S. Provisional Application 60/517,918, filed 7 November 2003. Both the priority date and the PCT filing date of the present application pre-date the publication date of Aminova. Accordingly, Aminova does not qualify as prior art to the present application. The Examiner's reliance on Aminova is clear error.

It would appear that the Examiner is somehow attempting to suggest that the obviousness argument is not actually based on Aminova, when he states that the claims are "unpatentable over Teichberg ... as evidenced by Aminova et al. ... ." *Final Office Action*, page 2 (emphasis added). The Examiner's use of the phrase "as evidenced by" would appear to indicate that he is trying to use Aminova merely to demonstrate the accuracy of some of his assertions in the rejection. Applicants assert that any use of Aminova in the obviousness rejection is impermissible and clear error. Moreover, it is also clear from the obviousness rejection that the Examiner is relying on Aminova in a substantive manner in making the obviousness rejection.

Indeed, the Examiner is using Aminova for all three required elements in the obviousness analysis: (1) teaching all the elements, (2) providing motivation and (3) demonstrating predictability. Accordingly, Applicants assert that the Examiner is in clear error by using Aminova substantively in the obviousness rejection. Finally, even if the Examiner is allowed to continue to use Aminova in the obviousness rejection, this reference in no way teaches or suggests what the Examiner is alleging. The Examiner's interpretation of Aminova is in clear error.

After Aminova is removed as a reference, Applicants assert that the Examiner cannot sustain the obviousness rejection. First, the collection of remaining references (Teichberg and Lu) fails to teach each and every element of the claimed invention; second, the Examiner has not identified any type of motivation that one of skill in the art would have in applying the teachings of Teichberg and Lu to subjects in need of neovascularization therapy. Finally, the Examiner has not identified any reasonable expectation of success or predictability in applying the teachings of Teichberg and Lu to promote neovascularization in subjects in need of such treatment.

The Examiner states that the method in Teichberg is "taught as being useful for reducing brain glutamate levels in patients having coronary artery bypass surgery, which is a treatment for severe atherosclerosis. Furthermore, a patient having said surgery would necessarily be in need of wound

healing … ." *Final Office Action,* page 3. In other words, the Examiner appears to be suggesting that the methods of Teichberg, which allegedly include administering oxaloacetate, pyruvate, o-ketoisocaproate, o-ketoisovalerate, o-keto-l3-methylvalerate to patients to reduce brain glutamate levels, would inherently treat wound healing. The Examiner's statement is a clear indication that the Examiner is using inherency in the obviousness analysis in that reducing glutamate brain levels inherently treats wound healing.

The use of inherency, however, is impermissible in an obviousness analysis, unless the inherency would have been obvious to one of skill in the art. *See Kloster Speedsteel AB, V. Crucible Inc.,* 793 F.2d 1565, 1576, 230 U.S.P.Q. (BNA) 81, 88 (Fed. Cir. 1986). "Inherency and obviousness are distinct concepts." *Id.* To sustain the rejection, the Examiner must establish that it would have been obvious to one of skill that promoting neovascularization would inherently occur in every patient in which one was trying to lower glutamate levels in the central nervous system. The Examiner has failed to establish this fact, and this failure is clear error. "Such a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination." *In re Rijckaert,* 9 F.3d 1531, 1533, 28 U.S.P.Q.2d (BNA) 1955, 1957 (Fed. Cir. 1993). "Obviousness cannot be predicated on what is unknown." *Id.* (quoting *In re Spormann,* 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (BNA) (C.C.P.A. 1966)).

At best, Teichberg discloses reducing glutamate levels in the central nervous system (see ¶0001 of Teichberg). Teichberg, however, does not disclose or suggest that glutamate levels are associated with either levels of HIF-1 or with neovascularization activity. Indeed, Applicants note that the Final Office Action states that "Teichberg fails to directly disclose the relationship between the glutamate concentration and HIF-1 mediated gene expression." *Final Office Action,* page 4. This statement, even though accurate, misses the point of the invention. The invention is administering one of the listed compounds to induce neovascularization in patients in need thereof. The rejection, therefore, should be based solely on the relationship between the listed compounds and neovascularization. Nonetheless, to the extent that the Examiner is correct in that the invention is somehow related to the relationship between glutamate and HIF-1 levels, the Examiner admits that Teichberg fails to disclose each and every element of the claimed invention.

The Examiner then attempts to tie in glutamate levels with HIF-1 levels by citing Aminova. Again, Aminova is not prior art to the application and cannot be used to supply missing elements in the Examiner's obviousness analysis. Specifically, the Examiner states that "Aminova teaches that HIF levels are higher at reduced glutamate levels (see Aminova, figure 5c)." This statement is thus a clear

indication that the Examiner is relying on Aminova to fill in the missing elements between glutamate and HIF-1 levels. This reliance on Aminova is clear error.

The Examiner also states that it would have been obvious "to utilize the composition of Teichberg in amounts significant enough to induce HIF-1 mediated gene expression since Teichberg teaches a composition for the reduction of glutamate, and Aminova teaches a relation between the concentrations of glutamate and HIF." *Final Office Action,* page 4. Further, the Examiner stated that "[t]here would be a reasonable expectation that Teichberg would use an effective amount of glutamate to induce HIF-1 mediated gene expression based on the evidence shown in figure 5c of Aminova wherein the relationship is identified." *Id.*

These comments are clear indications that the Examiner is using Aminova for both motivation ("Aminova teaches a relation between the concentrations of glutamate and HIF") and predictability or reasonable expectation of success ("[t]here would be a reasonable expectation that Teichberg would use an effective amount of glutamate to induce HIF-1 mediated gene expression based on the evidence shown in figure 5c of Aminova."). Aminova is not prior art to the present application, thus its use in providing motivation and predictability or reasonable expectation of success is clear error.

Moreover, if the Examiner continues to rely on Aminova in the obviousness analysis as merely providing evidence, Aminova does not even teach or stand for the proposition that he is asserting. Figure 5c of Aminova only shows that cells die as the concentration of glutamate increases. In Figure 5c of Aminova, the y-axis is labeled "% cell viability" and the x-axis is labeled "glutamate." Figure 5c is a dose response curve, where the "response" is cell death, not HIF-1 levels. If Figure 5c were demonstrating the Examiner's assertions, one of the axes of the figure would <u>have</u> to be labeled "HIF-1 levels," which it is not. Figure 5c of Aminova in no way shows or even suggests that HIF levels decrease in response to glutamate. The legend in Figure 5c that names "siHIF," which is presumably where the Examiner focused his attention, is a kill curve for a cell population that constitutively expresses HIF. Figure 5a and the "Experimental Procedures" sections confirm this interpretation when they disclose that HT22 cells were infected with retroviral vectors containing HIF. As the Examiner should know, infection of cells with a retrovirus indicates that HIF is constitutively and constantly expressed. Figure 5c therefore does <u>not</u> disclose that HIF levels are higher at reduced glutamate levels. Thus, to the extent that the Examiner is allowed to continue to rely on Aminova in the obviousness analysis, Aminova does not associate HIF levels and glutamate. Relying upon Aminova to demonstrate a relationship between glutamate and HIF-1, *i.e.,* to supply missing elements, is clear error.

In addition, to the extent the Office will permit the Examiner to continue to rely on Aminova to provide motivation and predictability in the obviousness analysis, the actual content of Aminova must be interpreted accurately, as one of skill in the art would interpret this reference. Aminova simply shows that increasing glutamate in cell culture kills every cell type tested (each cell type had an identically shaped dose response curve). Thus, Aminova, at most teaches that cell viability decreases with increasing glutamate concentrations. Aminova does not show "a relation between the concentrations of glutamate and HIF," thus Aminova would fail to provide any motivation or reasonable expectation of success in administering any of the listed compounds to a patient in need of neovascularization therapy.

Without relying on Aminova, however, the Examiner has not articulated the requisite motivation and predictability or reasonable expectation of success for combining Teichberg and Lu to somehow arrive at an invention of administering any of the listed compounds to patients in need of neovascularization therapy. Indeed, the Examiner fails to establish why one of skill would be motivated to administer the listed compounds to a patient in need of neovascularization therapy, without referring to Aminova. The Examiner also fails to establish why one of skill would consider it predictable to administer one of the listed compounds to treat neovascularization, without referring to Aminova. Accordingly, relying only upon references that qualify as prior art to the application, the Examiner has improperly sustained an obviousness rejection without an "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness[1]." This is clear error.

For the foregoing reasons, Applicants submit that the pending claims are not obvious in view of the references that qualify as prior art to the application. Indeed, claimed elements are missing from Teichberg and Lu, and the Examiner has provided no rationale for combining Teichberg and Lu with any predictability or expectation of success.

Respectfully submitted,

Date 9 March 2010 By /Todd B. Buck/

MORGAN LEWIS & BOCKIUS LLP
Customer Number: 09629
Telephone: (202) 739-3000

Todd B. Buck
Registration No. 48,574

[1] "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 418, 82 U.S.P.Q.2d (BNA) 1385, 1396 (2007) (quoting *In re Kahn,* 441 F.3d. 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006)).